

CAT HAIR, STANDARDIZED - felis catus hair injection, solution

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ALK-Abello, Inc.

ALLERGENIC EXTRACT

(STANDARDIZED CAT HAIR)

WARNING

This product should be used only by or under the direction of physicians experienced in administering allergens to the maximum tolerated dose and the emergency treatment of anaphylaxis, and only where adequate means for treating severe systemic reactions are immediately available.

This standardized cat hair extract is not interchangeable with non-standardized extracts, cat pelt extracts or with extracts labeled in allergy units per mL (AU/mL).

See Description, Warnings, and Dosage and Administration sections for further information.

Allergenic extracts may potentially elicit a severe life-threatening systemic reaction, rarely resulting in death¹. Because of the possibility of severe systemic reactions, the patient should be instructed in the recognition of anaphylactic symptoms, observed in the office for 20 to 30 minutes after each injection, and warned to return to the office if symptoms of an allergic reaction occur. Serious adverse events should be reported to the FDA MedWatch Program:

MedWatch

5600 Fishers Lane Rockville, MD 20852-9787, (1 -800-FDA-1088)

Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators, and the risk of severely complicating the treatment of systemic reactions should be carefully considered before a decision to treat is reached. Care should also be taken with patients with unstable or steroid-dependent asthma, or with underlying cardiovascular disease. Before administering this or any allergenic extract, physicians should be thoroughly familiar with the information in this insert, especially the Warnings, Precautions, and Adverse Reactions sections.

DESCRIPTION

Standardized cat hair extract is manufactured from source material obtained from the wash of cat hair clippings, which is then concentrated and absorbed onto powdered cat hair. Cat albumin and other serum-related non-Fel d 1 allergens, found in cat pelt extracts, have not been included in this extract. Cat albumin is not an important allergen for 80% of cat-sensitive patients². They are supplied as sterile solutions for scratch, intradermal or subcutaneous administration. The inactive ingredients are as shown in Table 1. Table 1 Allergenic Extracts, Inactive Ingredients

Extract Formulation	Ingredient	Concentration (%)
Glycerinated	Sodium Chloride	0.5
	Sodium Bicarbonate	0.25
	Glycerin	50 (v/v)

Standardized cat hair extracts containing 10 to 19.9 Fel d 1 units per ml are assigned 10,000 Bioequivalent Allergy Units per ml (BAU/ml) based on quantitative skin testing³. Standardized cat hair extracts containing 5 to 9.9 Fel d 1 units per ml are assigned 5,000 BAU/ml.

Isoelectric focusing (IEF) patterns of these standardized cat extracts have been shown to be predictive of the presence of non-Fel d 1 allergens. IEF has been adopted by the FDA as a release criterion. Therefore, all lots of Standardized Cat Hair extract are required to be compared by IEF to Center for Biologics Evaluation and Research (CBER) Cat Hair Extract Reference⁴.

Allergenic extracts must be diluted before use in intradermal diagnosis or in the initial stages of treatment.

CLINICAL PHARMACOLOGY⁵

The mode of action of allergenic extracts is under investigation.

The skin test reaction occurring in previously sensitized individuals is probably related to the interaction of antigen with IgE antibody and the subsequent release of histamine from mast cells. The therapeutic action of allergenic extracts may be related to the production of IgG (blocking) antibodies that remove allergenic proteins from the blood stream. Effective immunotherapy with allergenic extracts is usually associated with a shift in T-cell populations from a T_H2 predominant type to a T_H1 predominant population. This shift has been associated with changes in certain cytokines and other mediators. Immunotherapy also produces an initial rise in specific IgE levels, which then decrease as therapy continues.

Immunotherapy using cat extract has been studied by several investigators.

Generally, it is believed that hyposensitization with this product is helpful in reducing allergic symptoms associated with environmental exposure to cat allergens^{6,7}.

In skin test studies of ten patients who were determined to be allergic to cat, the average puncture test (using a bifurcated needle) to a Cat Hair Extract containing 10,000 BAU/ml produced a mean # E of 82.4 mm with a range of 61 to 110 mm and a mean # W of 15.6 mm with a range of 9 to 19 mm.

In this skin test study of cat-sensitive patients, the study subjects exhibited the following intradermal test responses:

		BAU/ml to elicit 50 mm sum of diameter of erythema reaction.	
Allergen	Number of Persons	Mean	Range
Cat Hair	10	0.015	0.0007-0.21

INDICATIONS AND USAGE

Standardized Cat Hair allergenic extracts are indicated for the diagnostic skin testing and immunotherapy of patients whose histories indicate that they experience allergic symptoms upon natural exposure to the specific allergens.

CONTRAINDICATIONS

The product is contraindicated for use in subjects who are not clinically allergic to the specified allergen, or who are not reactive to ALK-Abelló extract. No other absolute contraindications to immunotherapy with allergenic extracts are known.

However, the risk of serious systemic anaphylactic reactions to any potent allergenic extract suggests a number of preexisting conditions that should be considered relative contraindications. Among those conditions are acute infections, immune disease, severe cardiac disease pulmonary diseases such as asthma with a significant irreversible component, and treatment with β -adrenergic antagonist drugs ("beta-blockers"). See also Warnings, Precautions, and Adverse Reactions.

WARNINGS

See additional warnings given in the box at the beginning of this insert.

Do not use this extract or allow its use until you have read this insert, and have taken adequate precautions to prevent inadvertent dosage errors. See Dosage and Administration for further information.

Some patients are highly sensitive to allergenic extracts, and in such patients even a small skin test dose could result in a serious systemic reaction. Adequate means to treat such reactions must be immediately available, including the following equipment⁸: stethoscope and sphygmomanometer; tourniquets, syringes, hypodermic needles, and large-bore (14 gauge) needles; aqueous epinephrine HCl 1:1000; oxygen, intravenous fluids and the equipment for administering them; oral airway; diphenhydramine or similar antihistamine; aminophylline and corticosteroids for intravenous injection; and vasopressor.

Observing the following precautions will reduce the risk of serious systemic reactions:

- Do not begin immunotherapy without establishing the appropriate initial dose by skin testing (see Dosage and Administration), and do not inject the undiluted extract concentrate at any time unless tolerance has been demonstrated.
- When changing to an extract from a different manufacturer establish the proper dosage by skin testing.
- When changing to a different lot of extract, reduce the dose by 50-75%; this is particularly important after using an extract that is near its expiration date.
- Take care to properly prepare, label store and control all dilutions.
- Use caution in dosing of high-risk steroid-dependent labile asthmatics.

DO NOT GIVE INTRAVENOUSLY. After inserting the needle subcutaneously, but before injecting the dose, retract the plunger of the syringe slightly. If blood appears in the syringe, discard the syringe and its contents and repeat the injection at another site. Subcutaneous injection is recommended because intracutaneous or intramuscular injections are more likely to produce local reactions. Observe the patient at 20 to 30 minutes after injection, and be alert for the signs of impending reaction. Make sure the patient understands that serious delayed reactions can occur later on, how to recognize them, and what to do if they occur.

Patients who are receiving beta-blocking medication are high-risk patients for immunotherapy, because systemic reactions to the extract may be more severe in such patients⁹, and because the beta-blocker may impair the ability to reverse the reaction¹⁰ in such patients. This risk should be carefully weighed before a decision to treat is reached. Care should also be taken with patients with unstable or steroid-dependent asthma or with underlying cardiovascular disease.

This and any allergenic extract should be temporarily withheld or its dosage reduced under any of these conditions¹¹:

- When the patient has an unexpectedly severe local or any systemic reaction to the previous dose.
- If the patient is experiencing allergic symptoms such as rhinitis or asthma or is ill with flu or infection accompanied by fever.
- If an unusually long time has passed since the previous injection.
- If the patient is exposed to excessive amounts of clinically relevant allergen prior to therapy.

Allergic patients differ widely in their sensitivity to this or any allergenic extract, and no single dosage regimen can be recommended for all patients. Progression to the next higher dose requires tolerance of the previous one, and the regimen must be modified if any of the conditions described above occur. Such modifications should include weaker dilutions and smaller dosage increments.

PRECAUTIONS

General:

Patient compliance is an important consideration in the decision to initiate immunotherapy with any potent allergenic extract. Therapy should not be initiated if in the judgment of the physician the patient cannot be depended upon to respond promptly and properly to an impending adverse reaction, or to report such reactions.

Care must be taken to control the preparation, labeling, storage, and use of dilutions.

The ramifications of inadvertent overdosage are severe (see Warnings and Adverse Reactions), and so procedural safeguards such as training programs, color-coded labeling, storage controls, and auditing are recommended.

As with the administration of any parental drug, observe all aspects of aseptic technique. In both testing and treatment, use a separate sterilized needle and syringe for each individual patient, to prevent transmission of hepatitis and other infectious agents from one person to another.

Information For Patients:

The patient should be told to remain in the office for 20 to 30 minutes after injection, and be alert for the signs of impending reaction. The patient should be instructed that serious delayed reactions can occur later on and that these must be reported to the physician immediately. These reactions include swelling or tenderness at the site of injection, rhinorrhea sneezing, coughing, shortness of breath nausea dizziness wheezing, rash or faintness.

Drug Interaction:

Patients who are receiving beta-blocking medication are high-risk patients for immunotherapy, because systemic reactions to the extract may be more severe in such patients⁹, and because the beta-blocker may impair the ability to reverse the reaction¹⁰.

The patient should not take antihistamines prior to skin testing, since the pharmacological actions of such drugs might interfere with the skin test response.

Discontinue regular antihistamines for 3-10 days and contacting antihistamines such as Astemizole for as long as 60 days before skin testing¹². Also, be aware that the concurrent use of antihistamines during immunotherapy might mask an otherwise observable local reaction to an injection.

Carcinogenesis, Mutagenesis, Impairment Of Fertility:

No long term studies with this or any allergenic extract have been carried out to determine their effect on carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy Category C:

Animal reproduction studies have not been conducted with allergenic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Allergenic extracts should be given to a pregnant woman only if clearly needed.

On the basis of histamine's known ability to contract uterine muscle any reaction that would release significant amounts of histamine whether occurring from allergen exposure or immunotherapy overdose, should be avoided.

Nursing mothers:

It is not known whether this drug is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

Geriatric Use:

Clinical studies of allergenic extracts have not included sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use:

Clinical studies of allergenic extracts did not include sufficient numbers of pediatric patients to determine whether they respond differently from older patients. Other reported clinical experience has not identified differences in responses between pediatric and adult patients. In general, dose selection for a pediatric patient should be cautious, usually starting at the low end of the dosing range.

ADVERSE REACTIONS

Severe anaphylactic reactions to this extract can occur in extremely allergic patients and at any dosage level. Do not use this extract unless you are prepared to deal with these reactions, and until you have read and understood the warnings, precautions, and dosage and administration sections of this insert.

The most serious systemic reaction that can occur is anaphylactic shock which while rare, is life threatening and must be treated immediately. Among other systemic reactions that have occurred are laryngeal edema, fainting, pallor bradycardia, hypotension, bronchospasm, angioedema, cough, sneezing, conjunctivitis, rhinitis, and urticaria.

Should a serious systemic reaction occur:

- Inject 0.3-0.5 ml of 1:1000 epinephrine into the opposite arm; this may be repeated every 5 to 10 minutes, as a succession of smaller doses is more effective and less dangerous than a single larger one. Use a smaller dose for infants and children, in the range of 0.01 ml/kg of body weight.
- Apply a tourniquet proximal to the injection site; loosen it at least every 10 minutes interval.
- Inject no more than 0.1 ml of 1:1000 epinephrine at the injection site, to delay the absorption of the remaining extract.
- Beta adrenergic agonists or aminophylline may be helpful in alleviating bronchospasm and airway obstruction. Other treatments that may be of benefit include H₁ antihistamines (e.g., 1 mg/kg diphenhydramine) and glucocorticoids (e.g., 120 mg methylprednisolone).

These measures will almost always reverse the reaction but in the rare instances when they do not, then the full armamentarium of emergency medicine may be required, among them: direct laryngoscopy direct current cardioversion, tracheotomy, and intracardiac injection of drugs⁸.

The occurrence of a severe systemic reaction to an injection of this extract does not contraindicate further therapy, but the next dose given should be reduced by at least 90% and raised very slowly thereafter. If a pattern of systemic reactions- even very mild ones- appears, then the benefits of continued treatment must be carefully weighed against the substantial demonstrated risk.

Local reactions, even relatively severe but transient redness, swelling and discomfort, are the normal physiologic response to the allergens and to the volume of the fluid injected, and in their milder forms are not unexpected. Local reactions generally subside quickly and do not require treatment, but application of cold to the injection site or other symptomatic measures may be useful.

However, severe local reactions should be considered a warning of potential systemic reaction if that dosage is continued. Always reduce the dose substantially if such a local reaction occurs.

Overdosage:

See Adverse Reactions section.

DOSAGE AND ADMINISTRATION

Dilution

Allergenic extract concentrates must be diluted before use in intradermal skin testing or the initial stages of immunotherapy. As with any parenteral product, always use careful aseptic technique in preparing dilutions, assuring that the vials, diluents, and syringes are sterile, and that the dilutions are prepared under aseptic conditions. Sterile diluents that can be used include Normal Saline, Buffered Saline, 50% glycerin or Albumin Saline (HSA).

To obtain the concentrations required for intradermal testing or for the initial stages of immunotherapy, prepare serial 5 or 10 fold dilutions of the concentrate, to achieve the concentrations specified in Table 2 or 3, below. The relatively small 0.5 ml volume conserves the original concentrate, and is convenient because sterile diluent is readily available in prefilled 2.0 and 4.5 ml volumes.

Table 2 Examples of Ten-fold Dilution Series

Dilution Number	Add This Volume/Dilution of Extract	To this Diluent Volume	To Obtain Extract at the Following Concentration (BAU/ml)
0	Concentrate	—	10,000
1	0.5 ml concentrate	4.5 ml	1,000
2	0.5 ml dilution #1	4.5 ml	100
3	0.5 ml dilution #2	4.5 ml	10
4	0.5 ml dilution #3	4.5 ml	1.0
5	0.5 ml dilution #4	4.5 ml	0.10
6	0.5 ml dilution #5	4.5 ml	0.01

Table 3 Examples of Five-fold Dilution Series

Dilution Number	Add This Volume/Dilution	To this Diluent	To Obtain Extract at the Following
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	of Extract	Volume	Concentration (BAU/ml)
0	Concentrate	—	5,000
1	0.5 ml concentrate	2.0 ml	1,000
2	0.5 ml dilution #1	2.0 ml	200
3	0.5 ml dilution #2	2.0 ml	40
4	0.5 ml dilution #3	2.0 ml	8
5	0.5 ml dilution #4	2.0 ml	1.6
6	0.5 ml dilution #5	2.0 ml	0.32

For each vial, record the date of dilution on the label.

Skin Testing

Scratch or prick-puncture testing should be performed using the 10,000 BAU/ml concentrate, a negative control (diluent) and a positive control (histamine 1.8 mg/ml). Extract for intradermal testing can be prepared by diluting the concentrate with any appropriate aqueous sterile diluent, as described above. A 100 BAU/ml concentration is also available for intradermal testing. The following skin testing protocol can be recommended:

1. The location for both prick and intradermal testing is usually the flexor surface of the forearm. Use aseptic technique throughout.
2. Perform a preliminary skin prick test with the extract concentrate, by placing a drop of the extract on the skin and then using a needle to prick the skin gently through the drop. Use a normal diluent as negative control and histamine as a positive control. Read the test after 15 minutes. Patients reacting strongly to the prick test should be considered highly sensitive to the extract, and suitable precautions should be taken. A suggested grading system appears in Table 4. If the histamine control is negative, the possibility of skin non-reactivity must be considered.
3. Begin intradermal testing, generally starting at the 100 BAU/ml dilution if the prick test was negative, or at 0.1 or 0.01 BAU/ml if the test was positive or if no prick test was done. Use a separate, sterilized syringe and needle for each extract and each patient. Introduce the needle into the superficial skin layers until the bevel is completely buried, then slowly inject approximately 0.02 - 0.05 ml.
4. Measure the wheal and erythema after 15 minutes, and determine the degree of response to the injection, in comparison to the negative control. A suggested grading system appears in Table 5.
5. If the intradermal reaction is negative at the initial concentration, continue intradermal testing with 10-fold increments in the concentration until a clearly positive response has been obtained or a peak concentration of 100 BAU/ml has been tested, whichever occurs first.

Table 4 Skin Test Grading System¹²

Grade	Wheal Results
0	No Wheal/same size as negative
+	<Half the Histamine Diameter
++	Half the Histamine Diameter
+++	Same Size as Histamine Control
++++	Size of Histamine Control +2mm

Table 5 Intradermal Skin Test Grading System¹³

Grade	Mean Diameters (mm)	
	Wheal	Erythema
0	<5.0	<5.0
±	5.0-10.0	5.0-10.0
1+	5.0-10.0	11.0-20.0
2+	5.0-10.0	21.0-30.0
3+	5.0-10.0 or pseudopods	31.0-40.0
4+	>15.0, many pseudopods	>40.0

The interpretation of the skin response is based on the size of the wheal, the size of the erythema, and the appearance of irregular, spreading, pseudopodlike projections from the test area. The presence of the latter indicates marked hypersensitivity. A patient is considered sensitive to the test extract if there is a reaction of 1 + or greater at a concentration of 100 BAU/ml or less, providing that the 1 + reaction is in relation to the negative control.

Immunotherapy

Administer the extract solution subcutaneously, using a suitable sterile 1 ml syringe and a 25-27 gauge 1/4 to 5/8 inch needle. The injections are typically given in the lateral aspect of the upper arm.

Dosage of allergenic extracts is a highly individualized matter¹², and varies according to the degree of sensitivity of the patient, the clinical response, and tolerance of the extract administered previously.

A safe starting dose for any allergic patient is that dose which on intradermal testing produces a 1 + reaction. For most patients a starting dose that is 0.1 ml of 0.01 BAU/ml dilution of the extract concentrate should be well tolerated, although in some very sensitive patients a more dilute concentration may be required.

If no untoward symptoms are observed following the initial injection, the dose can be increased gradually for each subsequent injection until the injection volume reaches 0.6 -0.8 ml. Then begin using the next more concentrated ten-fold dilution, and proceed with this dosage pattern until the maintenance dose-defined as that dose that either relieves the patient's symptoms or is the highest that the patient can tolerate is reached. Care must be taken, however, in administering a volume greater than 0.2 ml of any extract in 50% glycerin; such injections can be painful to the patient due to the glycerin content.

After each injection, evaluate the patient's skin reaction and overall response to determine whether the next scheduled dose can be given:

- If a single dose results in more than a moderate local reaction (>50 mm wheal) within 1/2 hour, the same dose should be repeated at the next visit - or visits - until the patient has tolerated it.
- If any systemic manifestation of sensitivity occurs during or following a visit, or if a single dose results in an excessive local reaction (> 100 mm wheal) within 1/2 hour, the total dosage for the next visit should be reduced to half of the dose that caused the reaction.
- Delayed local reactions (occurring 24-48 hours after injection) are relatively common, and do not appear to predict difficulties with future doses. As a rule, therefore, dosage adjustment is not required in most instances. However, at the physician's discretion and for the comfort of the patient, if delayed large local reactions over 10 mm are reported, the subsequent dose should be held at the same level as the one causing the reaction.

The optimal interval between doses of allergenic extract has not been definitely established. However, as is customarily practiced, injections are given 1, 2, or 3 times per week until the maintenance dose of extract is reached. At this time, the injection interval may be increased to 2 weeks, then to 3 weeks and finally to 4 weeks depending on the clinical status. If the patient does not return for 6 to 8 weeks after the last injection, the dose should be reduced to 25% of the last dose.

If longer than 8 weeks, a dose reduction of one, two or three dilutions may be made depending on a consideration of the components and the patient's sensitivity. The dosage and the interval between injections may need to be modified according to the clinical response of the patient. When switching patients to fresh extract, the initial dose should be reduced to one-quarter of the previous dose.

Duration of treatment: Careful selection of allergens and cautious progression to maximally tolerated doses are important elements in the success of immunotherapy. The optimal length of treatment with allergen immunotherapy is unknown. A treatment period of 3 to 5 years is common, although continuation for longer periods may be appropriate¹³.

Allergenic extracts, as any parenteral drug product should be inspected visually for evidence of foreign material or discoloration prior to administration. Some variation in color is normal and a minor level of extract precipitate may occur with some extracts, but do not use the extract if there is any question of its condition exists.

HOW SUPPLIED

These allergenic extract concentrates are supplied as sterile solutions in rubber stoppered glass vials. The concentrate is available in 5, 10, 30 and 50 ml size serum vials for Immunotherapy at 5,000 BAU/ml and 10,000 BAU/ml; intradermal dilution is available in vial sizes of 1, 5 and 10 ml at a concentration of 100 BAU/ml; and the Scratch test products are available in 3 ml and 5 ml dropper vials at a concentration of 10,000 BAU/ml.

To ensure maximum potency for the entire dating period, extract concentrates contain 50% glycerin (v/v) unless otherwise instructed by the physician.

Diluted extracts, special mixtures and prescription treatment sets are available at tile request of the physician.

Storage: The extract concentrate and all dilutions should be kept refrigerated at 2-8°C. Do not freeze, and do not use the extract concentrate after the expiration date printed on the vial label. Extracts that contain less than 50% v/v glycerin are less stable,

LIMITED WARRANTY

We warrant that this product was prepared and tested according to the applicable standards of the FDA and was true to label when it left our hands. Because of biological differences in individuals, because this product is manufactured to be potent, and because we have no control over the conditions of use, we cannot and do not warrant either a good effect, or against an ill effect following its use. This label sets forth the complete and excluding statement of all the terms of any warranty, express or implied (including the warranty of merchantability) between ALK-Abelló, Inc., the prescriber, and the user of this product. Such representations and warranties shall not be varied, supplemented, qualified or interpreted by any prior course of dealing between the parties, or by any usage of trade unless specifically authorized in writing, signed by any officer of the corporation.

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Revised November 2003

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